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Ghrelin and nesfatin-1 levels and relationship with fertility hormones in obese women

Ghrelin, nesfatin-1, and fertility hormones in obesity

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Abstract
Aim: This study aimed to evaluate calorie intake, fertility hormones, ghrelin, and nesfatin-1 levels during the menstrual cycle (MC) in fertile women, and to determine possible the independent relationship between obesity and food intake, and the serum levels of fertility and adipokine hormones.
Material and Methods: Thirty normal weight and 30 obese women, all having apparently normal fertility, were studied. Calorie intake and serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone (fertility hormones), and ghrelin, nesfatin-1 were measured during the follicular (FP), midcycle (MP), and luteal (LP) phases of the MC.
Results: Calorie intakes were significantly higher in obese women compared with controls. Obese women showed lower FSH, LH, estradiol, ghrelin, and nesfatin-1 levels compared with normal women, whereas progesterone levels were similar between the two groups. The levels of ghrelin and nesfatin-1 increased gradually during the menstrual cycle, peaking at MP and declining gradually thereafter. With Spearman's correlation analyses in obese women, ghrelin showed a negative correlation with calorie intake and a positive correlation with FSH/LH/estradiol, whereas nesfatin-1 maintained a positive association with calorie intake and FSH and LH showed a negative correlation with LH/estradiol.
Discussion: It is not known, whether the fertility hormones in MC are associated with the appetite-regulating hormones, and whether these hormones differ between phases of the MC between obese or non-obese women.

Keywords
Obesity, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, ghrelin, nesfatin-1, menstrual cycle

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Introduction

Obesity is an important health problem among women of childbearing age worldwide and has many harmful effects on women's reproductive health and system. Menstrual dysfunction, anovulation, and infertility are also common in overweight women. Obesity may change the hormonal balance in the pituitary, ovaries, and endometrium of the reproductive system. Obese women have been reported to have increased insulin, triglycerides, and very-low-density lipoprotein (LDL), FSH, LH, estradiol, progesterone levels and decreased high-density lipoprotein (HDL) levels. Due to these changes, the hypothalamus-pituitary gonadal (HPG) axis is disrupted and different gynecological effects occur. Although adipose tissue is necessary for reproductive and normal developmental functions, in obesity, excessive fat causes significant reproductive disorders [1]. White adipose tissue is an important endocrine organ that regulates energy homeostasis and metabolism by secreting adipokines. Some of those are leptin, adiponectin, ghrelin, and nesfatin-1 [2]. Recently, ghrelin and nesfatin-1 have attracted the interest of many researchers.

Ghrelin is a peptide hormone that was first identified as an endogenous ligand for the growth hormone (GH) secretagogue receptor. It is mostly synthesized by the stomach and expressed at low levels in the pituitary, hypothalamus, pancreas, small intestine, and ovary. Ghrelin was first discovered to stimulate the release of GH in the pituitary, and was later found to affect feeding behaviors and energy metabolism. In addition, a relationship with the HPG axis has been demonstrated, and it is thought to affect the secretion of gonadotropins. Plasma ghrelin levels decrease in humans when obesity and energy intake increase, and increase in fasting state and anorexia nervosa [3].

Nesfatin-1 was found firstly as a novel satiety anorexigenic factor in areas of eating behavior of the hypothalamus and was shown to induce satiety and inhibit food intake. It is mostly synthesized by the hypothalamus and expressed at low levels in the reproductive organs, adipose tissue, and gastrointestinal tract [2,4]. It is known that nesfatin-1 has a positive correlation with BMI in humans. In most studies to date, serum nesfatin-1 levels were found to be significantly lower in obese individuals [4,5] and higher in very few studies [6]. Nesfatin-1 has been shown to be expressed in the pituitary gland, ovaries, and testicles in the reproductive system [7]. Nesfatin-1 is thought to play a role in fertility, but little is known about its regulatory mechanisms in the reproductive system.

The menstrual cycle (MC) is characterized by monthly rhythmic changes in female hormone secretion and women have different physical and emotional symptoms (e. g. depression, irritability, binge eating, mass gain) [8]. Fertility and adipose tissue hormones have a significant influence on dietary intake and appetite. Recently, an increase in total calorie and carbohydrate intake in women during the MC has been reported [9]. Considering the high energy levels required for reproduction, it is thought that ghrelin and nesfatin-1 may have a role in reproductive physiology. Studies also suggest that ghrelin has important effects on the HPG axis in the release of hormones in the reproductive system. Ghrelin stimulates LH and prolactin release or inhibits the secretion of GnRH, testosterone, and progesterone, as well as induces Leydig cell proliferation and luteal function. On the other hand, nesfatin-1 decreases LH and FSH mRNA expression in the pituitary [10]. It also affects circulating FSH, LH, and estradiol in a dose-dependent manner. Nesfatin-1 can increase and decrease circulating FSH and LH, respectively, when administered high-dose intracerebroventricular (ICV), and low-dose intraperitoneal (IP) [10,11]. In vitro, it increases ovarian progesterone secretion [12]. Circulating estradiol levels are also reduced by IP administration of nesfatin-1 [13].

With a cross-sectional study, we have tested the hypothesis of a possible independent relationship between fertility and adipokine hormones in normal or overweighted women during MC. These relationships will inform us about the role of adipose tissue hormones in reproduction.

Material and Methods

Sixty healthy women who were admitted to the Clinic of Obstetrics and Gynecology at the Cankiri State Hospital were enrolled in the study. The study was approved by the Ethical Research Committee of the University of Zonguldak Karaelmas/ Turkey (2011/07). All individuals were informed about the study and approved consent forms were obtained. Firstly, ages, height, weight, waist circumference widths parameters of the individuals were recorded, and their body mass index and BMI scores were calculated. Women were assigned to the obese group if their BMI were >30 kg/m2, and to the control (non-obese) group >20-24.9 kg/m2. The age range in those groups was 18 – 40 years, and their demographic features are presented in Table 1. Inclusion criteria were no pregnancy, age ≤18/≥45 years, no alcohol or smoke usage, no gynecological treatment with any drugs or contraceptives for the last 6 months, and no disease (such as adrenal hyperplasia, hyperprolactinemia, polycystic ovary disease, hypertension, diabetes mellitus, thyroid/heart disease, and cancers). Blood samples (5 mL) were obtained intravenously between 8 and 11 am after 12 hours of fasting. Ghrelin and nesfatin-1 are peptide hormones that can be broken down by serum proteases; therefore aprotinin (500 Kallikrein units/mL) was put into the blood tubes. The first sampling was done at the follicular phase (1st-3nddays). Subsequent samples were taken mid-cycle at (12th-16th days) and luteal phase (23th-27thday). Then they stored at –70 °C until further analysis of fertility and adipokine (ghrelin and nesfatin-1) hormones.

Normal fasting blood glucose (FBG) and serum insulin (FSI), triglycerides, HDL, LDL, and total cholesterol analysis were performed with Beckman Coulter DX800 auto analyzer (Beckman Coulter, Inc., CA, United States).

In the study, the participants recorded the foods and beverages consumed throughout the day to obtain the daily calorie, carbohydrate, protein, and lipid amounts of the individuals. They were also asked to record attributes such as diet name, amount consumed methods of preparation, and trademarks of existing products in recipes to provide accurate and detailed data. The National Food Composition Database TurKomp was used as the reference table, and DietitianPro® Software was used for calculations.

Serum levels of FSH, LH, estradiol, and progesterone were

determined using human enzyme-linked immunosorbent assay (ELISA) kits (Architect, Abbott Laboratories, IL) according to the manufacturer's instructions. The results were expressed as mIU/mL, pg/mL, and ng/mL, and the lower detection limits were 0.05 IU/L, 0.07 IU/L, 17.9 pg/mL, and 0.2 ng/mL, respectively.

Serum acylated-ghrelin and nesfatin-1 levels were analyzed using commercial human ELISA kits (Cat. No: A05106, SPI-BIO, France; Cat. No. EIA-NES-1, RayBiotech Inc., Georgia). The values were read at 410 nm and 450 nm using a microplate reader (BioTekMicroplate Instruments, USA) and were expressed as pg/ml and ng/ml, respectively (the lower limits 4 pg/mL and 0.1 ng/mL).

While evaluating the findings obtained in the study, the SPSS program (Statistical Package for Social Sciences 20.0, USA) was used for statistical analysis. The Mann-Whitney-U test and Spearman correlation analysis were used to compare differences between groups. The level of significance, p was 0.001 and all data in the tables were mean ± SD.

Results

The demographic features of the individuals are given in Table 1. There were no differences in age and MC duration (days), but were significant differences in BMI and waist circumference between the two groups. As expected, obese women had higher BMI and waist circumference.

Daily calorie intakes, carbohydrate amounts and FBG, FSI, triglycerides, LDL, and total cholesterol were significantly higher and HDL lower in obese women compared to controls. The amount of protein and lipid intake were not significantly different between the groups (Table 2).

In this study, we have determined the changes in fertility hormones and ghrelin, nesfatin-1 levels during the MC. For all women, profiles at the follicular phase (FP), mid-cycle (MP) and luteal phase (LP) were investigated. All determined steroids had the expected trends of menstrual phases in all women. During the menstrual cycle, FSH, LH, and estradiol levels were found lower in obese women than in controls, whereas, progesterone levels were found similar between the two groups.

Table 2 shows the dynamics of ghrelin and nesfatin-1 levels at FP, MP, and LP in participants with obesity and controls. Obese women showed lower ghrelin and nesfatin-1 levels compared with normal women. Their levels increased gradually during the stimulation with LH and estradiol, peaking at MP, and declined gradually thereafter in all women ($p<0.001$). Spearman's correlation analyses among variables were conducted for the obese women using ghrelin and nesfatin-1, which are presented in Table 3. When we have compared ghrelin levels and calories at the FP, MP and LP, we have found a significant negative correlation. Also, positive correlations were determined between ghrelin and FSH/LH/estradiol. There was a significant negative correlation between nesfatin-1 levels and calorie intake, positive correlation between nesfatin-1 and LH/estradiol, in the study. No correlations were found between ghrelin/nesfatin-1 and progesterone.

Table 1. Demographic features of the control and obese groups

	Control	Obese
N	30	30
Age (year)	26.3±7.2	28.2±6.8
BMI (kg/m2)	23.8±3.1	32.3±4.5*
Waist circumference	64.42±8.22	87.32±7.15*
Menstrual cycle duration (days)	28.7±3.2	27.1±4.3

BMI: Body mass index, *P-value: p<0.001

Discussion

The hormonal changes during the MC have a significant influence on calorie intake and appetite. In normal-weight women, an increase in energy intake and output during the LP of the MC has been reported [9]. In this study, an increase in total calorie and carbohydrate intake was determined in obese women. It was also found that those parameters increased in LP and FP

Table 2. The biochemical findings of the control and obese groups during the menstrual cycle

	Follicular phase (FP) Control	Follicular phase (FP) Obese	Midcycle phase (MP) Control	Midcycle phase (MP) Obese	Luteal phase (LP) Control	Luteal phase (LP) Obese
Calories (kcal)	1357±521	1809±782*	1281±312	1656±684*	1567±129	1896±783*
CHO (g)	186±14.8	257±33.2*	174±12.7	204±28.1*	190±25.4	265±34.9*
Protein (g)	65±12.3	71±26.8	58±17.8	64±31.4	70±32.6	72±41.3
Lipid (g)	51±11.2	56±12.8	47±13.6	49±18.3	52±24.8	54±22.5
FBG (mg/dL)	86.32±7.18	116.45±9.72*	84.47±6.82	114.71±8.26*	83.27±9.37	109.57±10.3*
FSI (µU/mL)	8.2±2.15	12.6±8.7*	7.3±1.87	11.3±6.8*	10.1±3.52	13.4±6.9*
Triglycerides (mg/dL)	85.71±54.5	134.65±62.8*	80.37±32.6	127.48±57.3*	90.27±39.8	145.42±71.3*
HDL (mg/dL)	57.5±5.2	41.3±3.8*	51.4±4.9	38.7±4.3*	65.8±8.1	48.9±7.2*
LDL (mg/dL)	121.3±14.3	154.2±16.5*	142.3±37.8	166.6±26.3*	109.4±12.5	134.3±19.7*
Total cholesterol (mg/dL)	158.76±27.83	207.57±42.2*	146.41±19.23	189.32±59.4*	174.19±35.67	216.43±64.3*
FSH (mIU/mL)	5.56±1.59	3.45±2.04*	6.68±1.25	4.91±2.17*	3.67±1.84	2.58±1.71*
LH (mIU/mL)	6.8±3.38	3.5±2.48*	16.8±2.27	11.8±1.98*	10.8±2.56	6.4±3.69*
Estradiol (pg/mL)	37.28±11.7	24.81±22.2*	107.83±13.7	89.48±19.4*	55.18±21.3	39.57±17.8*
Progesterone (ng/mL)	0.25±0.32	0.28±0.28	0.48±0.32	0.56±0.28	36.27±4.84**	37.79±5.36**
Ghrelin acylated (pg/ml)	41.52 ± 19.41	32.39 ± 8.62*	56.82 ± 19.41**	43.62 ± 7.46*,**	46.38 ± 12.83	35.83 ± 7.84*
Nesfatin-1 (ng/ml)	2.37±1.27	1.43±1.04*	4.15±0.98**	3.26±1.28*,**	3.69±1.13*	2.93±1.39*,**

Results are represented as mean ± SD. CHO: Carbohydrates, FBG: Fasting blood glucose, FSI: Fasting serum insulin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, *P < 0.001, significantly compared with the control; **P < 0.001, significantly compared with the FP

Table 3. Spearman correlation coefficients between ghrelin, nesfatin-1, and measured parameters in obese individuals

Variables	Ghrelin		Nesfatin-1	
	rs	p*	rs	p*
Calories (kcal) FP	-0.379	0.015	-0.356	0.013
Calories (kcal) MP	-0.394	0.014	-0.391	0.015
Calories (kcal) LP	-0.386	0.015	-0.382	0.016
FSH (mIU/mL) FP	0.412	0.006	0.215	0.324
FSH (mIU/mL) MP	0.452	0.005	0.198	0.298
FSH (mIU/mL) LP	0.401	0.011	0.186	0.312
LH (mIU/mL) FP	0.358	0.003	0.399	0.018
LH (mIU/mL) MP	0.421	0.024	0.402	0.021
LH (mIU/mL) LP	0.388	0.008	0.408	0.024
Estradiol (pg/mL) FP	0.376	0.003	0.392	0.016
Estradiol (pg/mL) MP	0.419	0.023	0.425	0.036
Estradiol (pg/mL) LP	0.384	0.004	0.412	0.032
Progesterone (ng/mL) FP	-0.164	0.274	-0.132	0.254
Progesterone (ng/mL) MP	-0.079	0.612	-0.152	0.247
Progesterone (ng/mL) LP	-0.394	0.005	-0.382	0.004

FP: Follicular Phase, MP: Midcycle, LP: Luteal Phase, p: statistical significance index. rs: Spearman's rho coefficient. * Significance set at $p \leq 0.05$ for all analyses.

compared to MP in obese women. Due to insufficient intake of micronutrients such as vitamin B6, calcium, magnesium, and potassium, high-energy diet consumption is thought to occur during these phases of menstruation in women [14]. Hormones such as leptin, ghrelin, and nesfatin-1, which regulate energy homeostasis, may also affect this situation [9].

We found a statistically significant difference between the groups and MC stages in the levels of ghrelin and nesfatin-1, which are the adipokine hormones examined in this study. Serum ghrelin and nesfatin-1 levelswere decreased in MC in obese women and an inverse relationship with calorie intake was observed. Ghrelin has various functions in the regulation of food intake and energy metabolism, and excessive food intake has an appetite-reducing effect by compensating with ghrelin levels [3]. Low levels of ghrelin have been found in obesity and our result is consistent with those [15,16]. It is known that nesfatin-1 levels increase during food intake, thus reducing food consumption and mass gain [2,6]. Studies on circulating nesfatin-1 levels in obese individuals are inconsistent. Abaci et al. [4] found significantly lower serum nesfatin-1 levels in obese children compared to the control group. Dokumacioglu et al. [5] showed that serum nesfatin-1 levels were lower in the obesity group compared to the control group. Anwar et al. [6] found in obese individuals that serum nesfatin-1 levels in the obese group were significantly higher than in the control group.

In this study, we followed changes in fertility and adipokine hormones during the MC. The hormone profiles of obese and non-obese women were compared during the MC at FP, MP and LP. During the MC, a decrease in the levels of FSH, LH, and estradiol and gradual increase in progesterone levels were found in all phases. Changes in ghrelin and nesfatin-1 during the MC were significant. Obese women showed lower ghrelin and nesfatin-1 levels compared with normal women. Their levels increased gradually during the stimulation with LH and estradiol, peaking at MP, and declined gradually thereafter in all women. There is a complex interaction between female reproductive physiology and adipokine hormones that affect the HPA axis [3]. Although adipokines have significant effects on the reproductive system, few studies have evaluated the possible effects of adipokines during MC. Published data on changes in ghrelin levels during MC are inconsistent. Dafopoulos et al. [17] found no change, but Sramkova et al. [18] showed a tendency towards a decrease in ghrelin levels in MP. Dafopoulos et al. [19] reported a significant negative correlation between ghrelin and estradiol levels in FP. In addition, many studies have shown that estrogen plays a role in the regulation of ghrelin secretion. Ghrelin levels have been reported to increase with the use of estrogen-containing oral contraceptives [20]. There are conflicting data in the literature regarding the effect of estrogen therapy on serum ghrelin levels. Di Carlo et al. [20] administrated exogenous estrogen to postmenopausal women and determined increased ghrelin levels in those. Nevertheless, Chu et al. [21] have shown significant reductions in ghrelin levels with estrogen treatment in postmenopausal women. In our study, it has been determined the positive correlations between ghrelin and FSH/LH/estradiol, especially in MP. No correlations were found between ghrelin and progesterone. Consistent with our findings, it has been reported that ghrelin stimulates LH and prolactin-releasing in the pituitary [7].

Animal studies have shown that estrogen/LH plays a role in the regulation of nesfatin-1 secretion. In an experimental study in mice, it was reported that estradiol and progesterone significantly increased/or decreased nesfatin-1 mRNA expression in cultured pituitary tissue, respectively [22]. Similarly, Sun et al. [23] showed that nesfatin-1 mRNA expression in the ovariectomized mice oviduct was significantly reduced, but the injection of 17β-estradiol increased again its expression. On the other hand, administration of nesfatin-1 decreases the expression of LH and FSH mRNA in the pituitary and also affects circulating FSH and LH in a dose-dependent manner (high/low dose may increase/or decrease) [12,13]. Literature data on nesfatin-1 levels during MC are limited. Demir Caltekin et al. [24] showed that nesfatin-1 levels were lower in lean women in FP of MC, with a significant negative correlation between nesfatin-1 levels and BMI. However, Ademoglu et al. [25] found that obese women had higher levels of nesfatin-1 in FP of MC. In addition, in a study conducted in pubertal female rats, it was observed that the expression of nesfatin-1 and LH increased in parallel in the hypothalamus. In our study, we found significant positive correlations between nesfatin-1 levels and LH/estradiol levels. No relationship was found between nesfatin-1 and progesterone.

Conclusion

Our results revealed decreased levels of adipokines in obese women during the physiological menstrual cycle. Their levels increased gradually during the stimulation with LH and estradiol, peaking at MP, and declined gradually thereafter in all women. More research is needed to better understand the reasons for these changes in ghrelin and nesfatin-1 throughout the menstrual cycle . This would also help understand why adipokine levels were increased or decreased during the phases of MC in normal or obese women.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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